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Provisional Application Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c).

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Docket Number	M-12928 V1 US	Type a plus sign (+) inside this box

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TITLE OF THE INVENTION (280 Characters Maximum)

"HbA1c Assay System"

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ENCLOSED APPLICATION PARTS (Check all that apply)

- ☒ Specification — Number of Pages 6
- ☒ Drawings — Number of Sheets 5
- ☐ Small Entity Statement
- ☐ Other: (Specify) _____

METHOD OF PAYMENT (Check one)

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The invention was made by an agency of the United State Government or under a contract with an agency of the United States Government.

☒ No
☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted:

Signature: K. Alison de Runtz Date: Nov. 5, 2002

Typed or Printed Name: K. Alison de Runtz Reg. No. 37,119

☐ Additional inventors are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

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HbA1c Assay System

Inventor:
Arvind N. Jina

Background of the Invention

The present invention relates to test strip and test meter structures and methods for the determination of the amount of irreversibly glycated hemoglobin, or HbA1c, present in a sample of blood, relative to total hemoglobin.

HbA1c is a glycated hemoglobin formed by binding between an amine group of hemoglobin and the glucose aldehyde group, for example between the amino group of the N-terminal valine of the ß-chain of hemoglobin and the glucose aldehyde group. The binding reaction first forms a Schiff's base and then a stable ketoamine by Amadori rearrangement. The rate of HbA1c formation is directly proportional to the concentration of glucose in the blood. The percentage of HbA1c (i.e. the amount of glycated hemoglobin relative to total hemoglobin in the blood) has come to be taken as a measure of the level of blood glucose control a diabetic has maintained for a period of two or three months prior to the measurement. As such, percentage HbA1c has become an important result by which health care providers can assist diabetics in their care.

There are many known assays that can be used to determine HbA1c percentage. In recent years research efforts have focussed on creating assays that are both highly accurate and fast. However, known HbA1c assays typically require a series of steps involving the treatment of a blood sample (for example for cell lysing) and the subsequent separation of blood components. Such steps do not lend themselves to test systems that are easy for diabetics to use in self-care situations.

In the health care context, a diabetic patient is typically guided by a physician to obtain an HbA1c measurement when the physician realizes the need for such information during an office visit. The patient then provides a blood sample to a laboratory and results are returned to the physician hours or days later. This time lag between the patient's visit and the result of the test requires that the health care

provider review the result long after the patient has left the office. If the provider believes that further consultation with the patient is required in light of the test result, the patient must be contacted again.

Currently, there is a device sold under the name "A1c NOW" by Metrika, Inc. of Sunnyvale, California. This handheld and disposable device (based on technology described in U.S. Pat. No. 5837546 entitled "Electronic Assay Device and Method," incorporated herein by reference) is said to provide an HbA1c test result in eight minutes using a relatively small sample of blood. The A1c NOW device is an example of the market demand for a fast method of providing an HbA1c result for either home or doctor's office use.

Summary of the Invention

The present invention includes a test strip for use in the *in vitro*, reflectance photometric, determination of HbA1c, the strip having a relatively simple structure, and the method of determining HbA1c using the strip. The system of the invention also includes a low cost meter containing an optical detection system into which the disposable test strip is inserted for reading.

Detailed Description of the Invention

The present invention is directed to a strip and meter system for the reflectance photometric determination of HbA1c. The system is used in a manner similar to blood glucose measuring systems of the strip-and-meter type now commonly used by diabetics for glucose self-monitoring. The presentation of the assay in this manner makes the system seem familiar and easy to use for diabetics and their health care providers.

In this invention, the HbA1c meter is the 'instrument' component of the HbA1c monitoring system. The meter is a handheld device that measures the electrical output from an optical test of a HbA1c test strip that is reacting with the HbA1c in a whole blood sample. The output is created using an optical system of the

type well known in the art of blood glucose testing, as further described herein. This electrical output is then converted into % HbA1c using built-in calibration algorithms and displayed to the user.

The design of the HbA1c meter integrates analog and digital circuitry, off-the-shelf electronic and optical components, commercially available mechanical components and a unique mechanical design, including a "door" or cover positioned over the strip receiving portion of the meter. Overall control of all meter functions includes the user interface and measurement subsystem. Communications and control of the test will be done by an internal microprocessor.

The HbA1c test of the invention can be performed easily by a user in a single step operation. This minimum amount of user intervention where there is no sample manipulation or sample preconditioning makes the system particularly useful.

Figures 1-6 show the meter structure of the invention. In a first step, the meter is turned on using "on" button 40, and door 10 (Fig. 1) is opened to permit the insertion of test strip 30 (Figs 2-3). Alternatively the meter can be turned on automatically by insertion of the test strip. In this case the strip end that is inserted contains a conductive coating well known in the prior art. The conductive layer serves to close an open switch circuit in the meter causing it to turn on. In this preferred embodiment, the door is mounted via hinge 20. The test strip is then inserted into the meter as shown in Figure 2. The meter may includes a display 60.

At this time, the user will obtain a small (hanging) blood drop (< 10 microliters) using a lancing device as is well known in the art. The blood sample is then applied to the application pad on the test strip. Two variations of possible test strip structures are shown in Figures 4-6, and discussed in greater detail below.

Once the blood sample has been applied to the test strip positioned in the meter, the user will wait a short period of time for the sample to penetrate the strip structure and for cell lysing to occur, for example for about 15-30 seconds. The door is then closed and the test proceeds. A result can be obtained in about 3 -5 minutes.

As mentioned, the meter of the invention includes a specially designed door. This door has two specific functions. The first is to block extraneous light from

causing interference in the optical measurements, and so it is preferred that the door be made from opaque material. The second function is to hold the strip down and simultaneously depress and cause the rupture of a pouch/blister (integrated with the test strip) containing an eluting solvent such as a buffer solution when the door is closed.

Two strip embodiments of the invention are described below, each of which can incorporate the solvent-containing pouch/blister.

Optical Meter with Two LEDs

In a first embodiment, the meter will contain no moving parts other than, for example, "on" button 40 and calibration code selection button 50. The optical meter will contain a light detector and 2 light emitting diodes ("LEDs," not shown) emitting different wavelengths of light, one each being positioned within the meter housing to determine the glycated Hb and the non-glycated hemoglobin. The value of the glycated Hb will be calculated and calibrated to reflect the % HbA1c. A test strip for use in this embodiment is shown in Figures 4A and 4B.

The test strip of Figures 4A and 4B includes a test strip handle 5, and a solvent reservoir/pad 4. The user can either apply buffer solution to pad 4, or the elution buffer can be carried in a "blister pack" affixed this portion of the strip (not shown, however, see Figure 5). The pouch or blister can be made to hold the eluting solvent alone or absorbed into a soft absorbent pad. Figure 4 further shows a sample application well 3, which will include a hemolysis reagent zone positioned immediately below the sample application well opening. Once sample has been applied and permitted to penetrate through the hemolysis zone, buffer is applied to pad 4, and the buffer elutes the lysed sample. The test strip further consists of a wicking membrane striped in one area with a glycated Hb capture zone 2, for example using boronate chemistry, immunoassay reagent or other suitable binding ligand known in the prior art. The hemolysis reagent is also known in the art. As the buffer elutes sample components down the strip, hemoglobin components not captured at zone 2 will continue on to zone 1 which has been preferably treated to capture non-glycated hemoglobin using reagent chemistries such as specific antibodies, haptoglobin or other suitable ligands known in the art.

Since the hemoglobin and glycated hemoglobin capturing areas of the strip are side-by-side, LEDs can be positioned beneath each for the purpose of obtaining the necessary optical signal for processing of the result using the microprocessor.

Optical Meter, Single LED Embodiment

The device of the invention can be further simplified by modifying the arrangement of the capture zones on the test strip in a way that permits the use of a single LED emitting two distinct wavelengths of light and a light detector and sequential measurements, rather than two LEDs in side-by-side arrangement. In this second embodiment of the invention the meter is otherwise virtually the same as in the first embodiment. Thus, in a second embodiment, the test is more highly integrated and simple. As with the first embodiment, the test strip will include a buffer elution pad for manual application of eluent (Figure 5A). Alternatively, blister pack 70 containing an elution buffer can be positioned in this area of the strip (Figure 5B). The blister pack is ruptured on closing the meter door for example by including a sharp point on a portion of the door that contacts the blister pack as the door is closed. Alternatively, the blister pack may be designed to include an absorbent pad containing the eluting buffer or solvent that is easily ruptured as pressure is applied by closing the door.

In this second embodiment, a hemolysis layer/zone is positioned below the sample application well and a glycated Hb capture zone is positioned below the hemolysis layer/zone (Figure 6) or they can be integrated to form a single reagent zone. In this case, as the sample is added it is hemolysed by the hemolysis reagent (known in the prior art). A reading is immediately taken using an LED positioned below the strip and Hb capture zone, which reading once calculated and calibrated will correspond to the Total % Hb. Upon hemolysis the glycated Hb becomes bound to the glycated capture zone. Addition of an elution buffer either via a ruptured blister pack or manually adding a buffer causes the unglycated Hb to be chromatographed or eluted away from the glycated capture zone by capillary action. At this instant a second reading is taken which will correspond to the % glycated Hb. The value of the glycated Hb will be calibrated to reflect the % HbA1c.

Numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the general scope of the invention, meters and test strips may be practiced other than as specifically described herein.

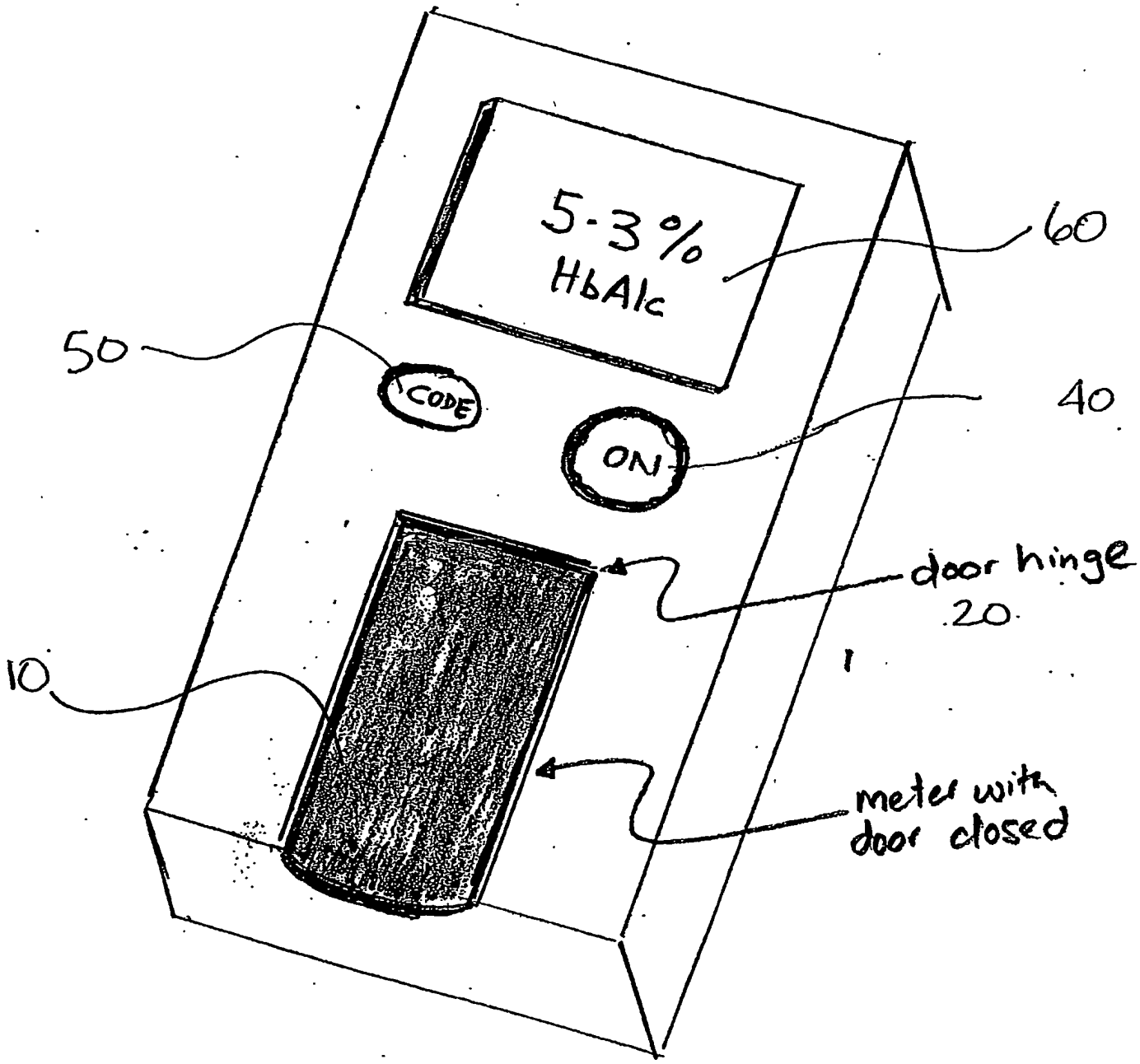
5-3%
HbAlc
60
50
CODE
40
ON
door hinge
20
10
meter with
door closed

Fig 1

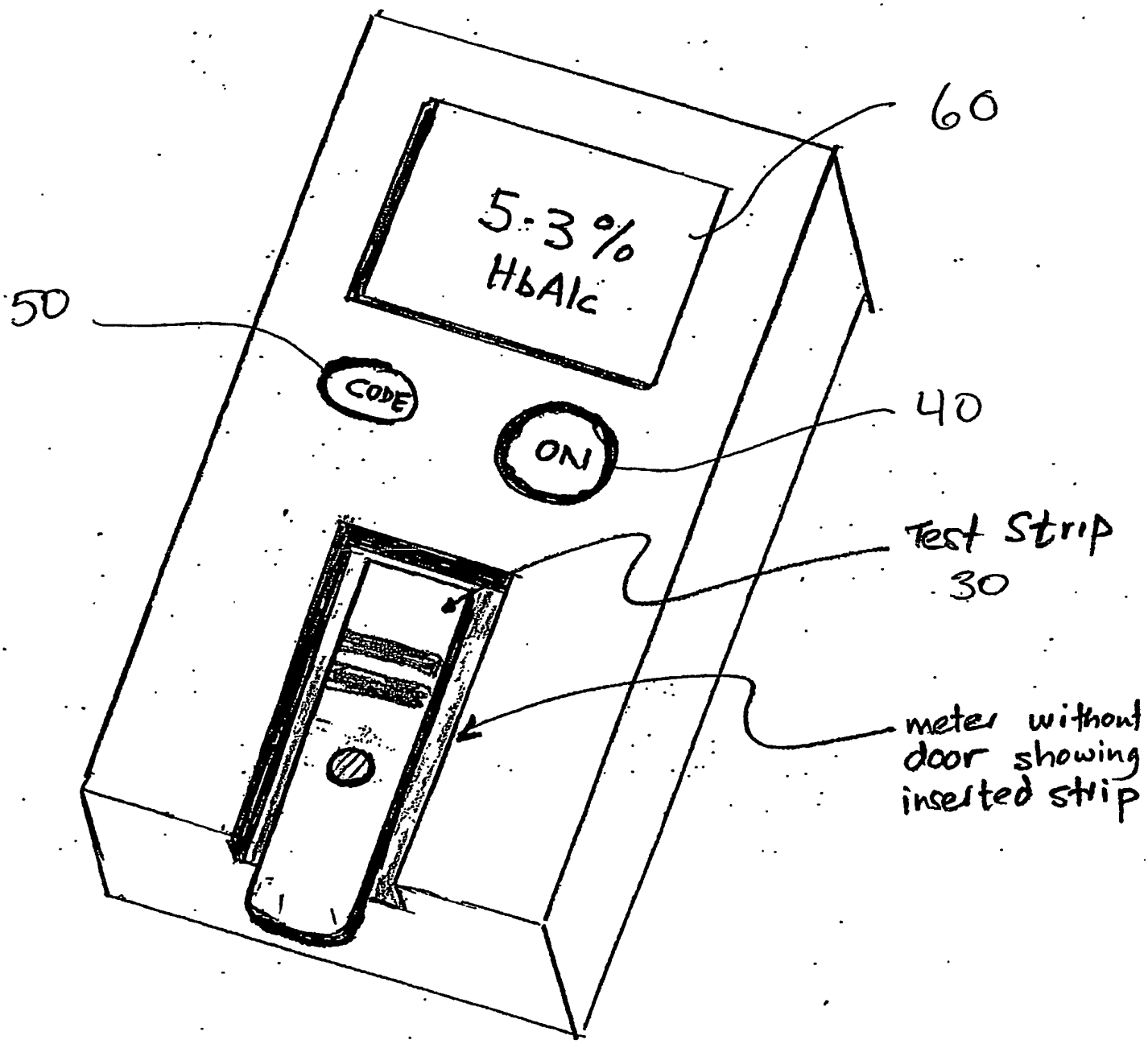
60
5.3%
HbAlc
50
CODE
ON
40
Test Strip
30
meter without
door showing
inserted strip

Fig 2

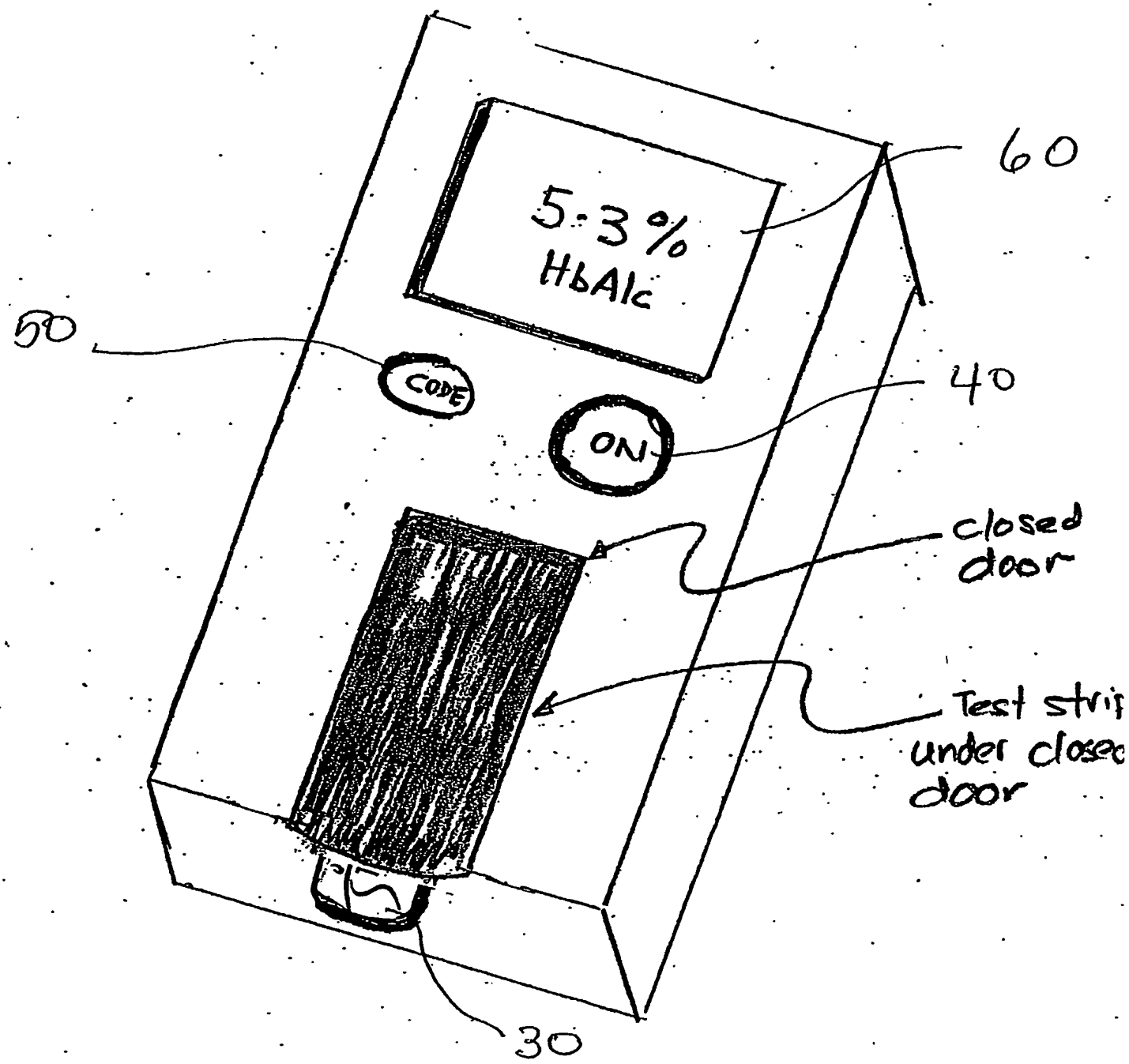
5.3%
HbAlc
60
50
CODE
ON
40
closed
door
Test strip
under closed
door
30

Fig 3

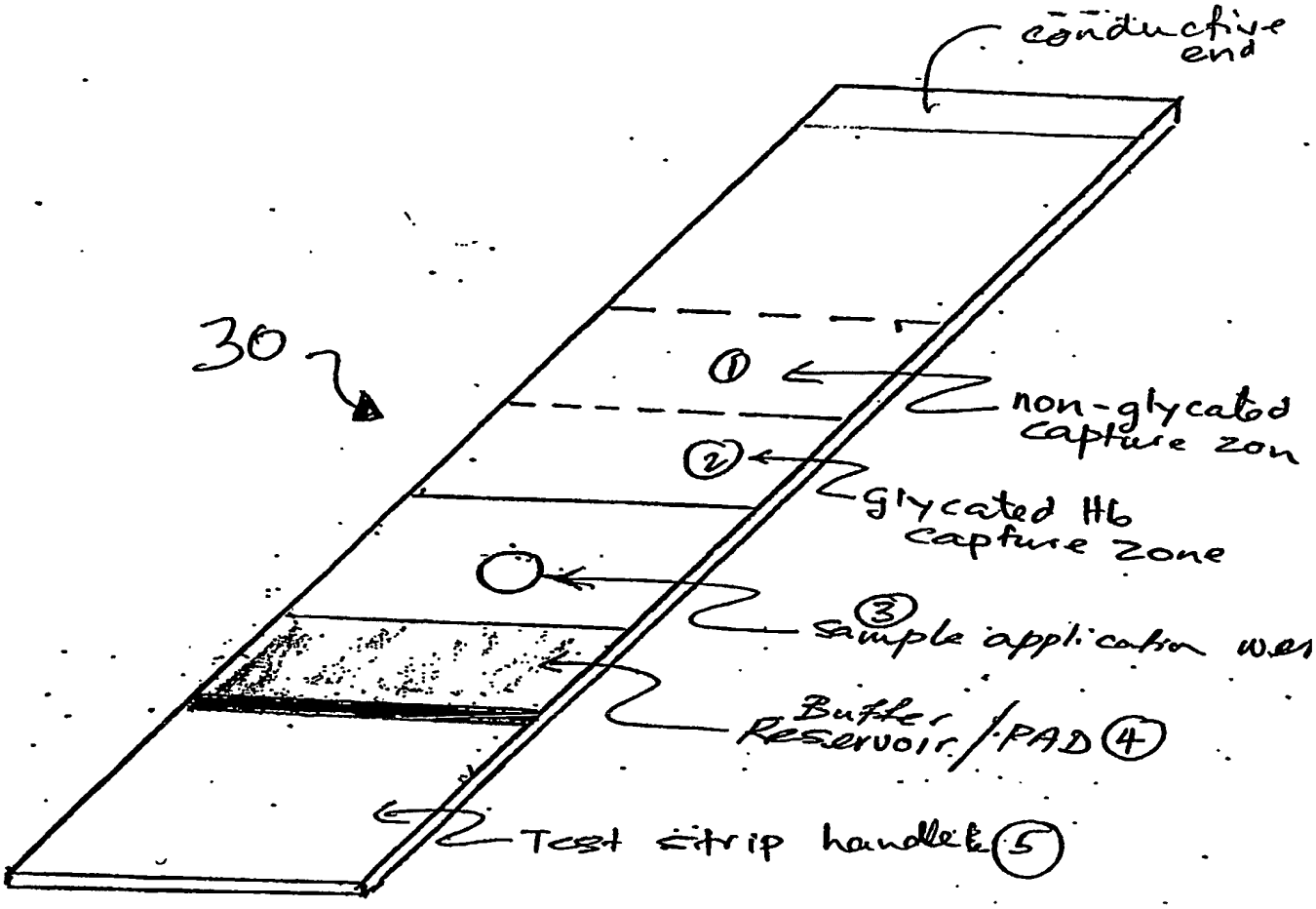

FIG. 4A

ed

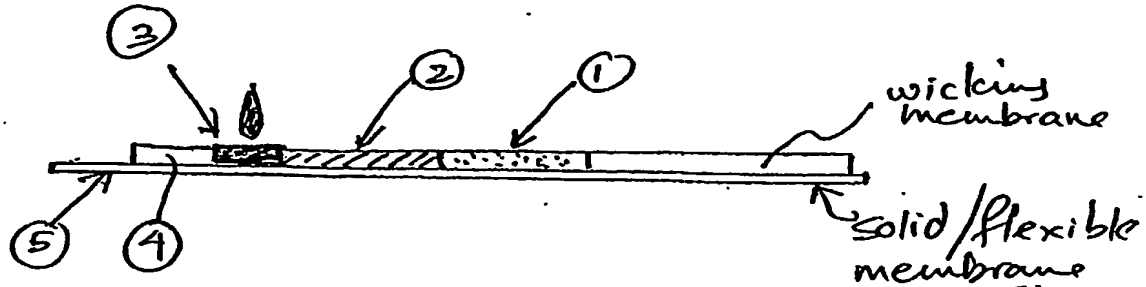

Fig 4B

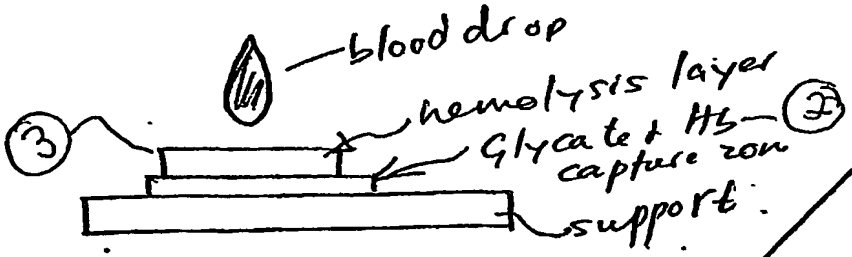

Fig 6

Fig 5A

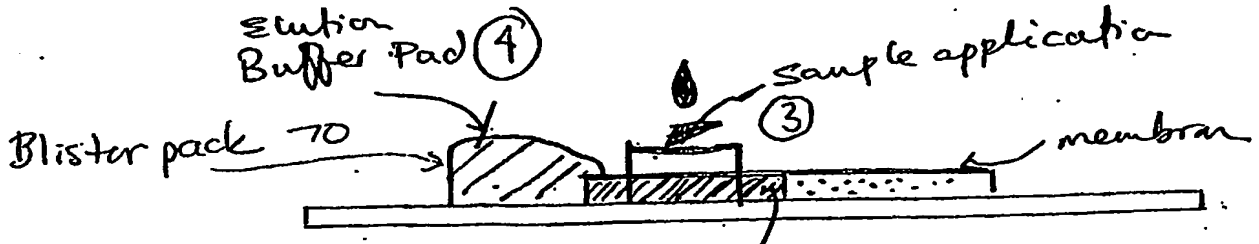

Fig 5B

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